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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,814	08/22/2007	Patrice Marche	045636-5083	7396

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MORGAN LEWIS & BOCKIUS LLP (WA)
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
09/23/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,814	MARCHE ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *23-35* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *23-35* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's reply filed 06/23/2011 is noted. Claims 23-35 remain pending in the application. The objection to the Sequence Listing is withdrawn in view of Applicant's replacement Sequence Listing supplied 06/23/2011. The rejections under 35 USC 103 made in the Office action mailed 02/23/2011 are maintained for the reasons of record.

Response to Arguments

Applicant's arguments filed 06/23/2011 have been fully considered but they are not persuasive. Arguments submitted by Applicant's representative and the arguments presented in the declaration of Dr. Pasqual (both submitted 06/23/2011) are similar and will be addressed as one. In addition, the Examiner has reviewed Dr. Pasqual's previous declarations submitted 01/11/2011 and 04/29/2010.

As an initial matter, the Examiner would like to point out that the only apparent *relevant* difference (i.e. the only difference that might be expected to affect yield of amplification product) between the method as claimed in claims 23 and 24 and the method of Pasqual is the following: Pasqual did not perform the elongation steps (plural) for 10 minutes; Pasqual performed only a *final* elongation step (singular) for 10 minutes. All the other differences (mouse DNA versus human DNA, Southern blot versus direct visualization on a gel) would not have been expected to increase the yield of PCR product. This is the essential crux of Applicant's arguments in the reply filed 06/23/2011: that one of skill in the art would not have expected modifying Pasqual's

method as set forth in the rejection would give sufficient yield to allow direct visualization of the amplified product on a gel.

Along these lines, the Examiner would like to point out that it was *taught* in the prior art that the longer the desired target to be amplified, the longer the extension time should be (Kolmodin, page 48, item 29). Hence, it would not have been expected that increasing the extension time would increase the yield of a long amplification product.

Turning now to Applicant's arguments filed 06/23/2011, which reiterated arguments made in the declaration filed 01/11/2011, Applicant asserts that one of skill in the art would not have been motivated to modify the Pasqual method to arrive at the claimed invention, because one of skill would not have expected such modification to be successful. That is, what is argued here is a reasonable expectation of success. Applicant rationale is as follows:

(1) Cheng (a rebuttal reference relied upon by the Examiner at page 16, Office action of 02/23/2011) used 37 ng of genomic DNA (gDNA) to amplify long fragments of the β-globin gene and was able to visualize the product directly on a gel (figure 5). Note from Cheng figure 5 that this is equivalent to ~10^4 copies of the genome.

(2) Cheng, however, was amplifying a target present in every copy of the genome, whereas Applicant's method is amplifying targets present in only *some* copies of the genome. More specifically, to have ONE copy of any particular TCR rearrangement, between 615/2 and 1968/2 copies of diploid genomes would be needed (declaration of 06/23/2011, item 9). Applicant calculates that, in order to have the same number of copies of template as Cheng (i.e. from Cheng's figure 5, 10^4), one would

need 37 ng X 615 = 22.755 µg of genomic DNA (declaration of 06/23/2011, item 9). Hence, Applicant argues that one of skill would have assumed that in order to modify Pasqual's method to arrive at the claimed invention, one would need to use 22.755 µg of genomic DNA in the PCR reaction. Implicit in this argument is the assertion that one of skill in the art would have considered 10^4 copies of template to be the minimum amount of template that would allow visualization of the amplified product of that template directly on a gel.

(3) Applicant asserts, based on an experiment performed by Dr. Pasqual in the declaration of 01/11/2011, that this amount of genomic DNA would inhibit PCR (see figure 1 of that declaration).

Thus, Applicant concludes that one of skill in the art would not have expected it possible for the claimed invention to work, since in order to have enough copies of template to amplify, one would need to use so much genomic DNA that the PCR would not be successful.

This argument is not persuasive for the following reasons:

First, in order for one of skill in the art to have been discouraged for the reason Applicant suggests (i.e. inhibition of PCR by increasing concentrations of genomic DNA), it would have had to have been *known* in the prior art that PCR efficiency was inhibited by high concentrations of genomic DNA. Applicant has provided no citation of any reference or any other evidence that such a problem was *known* in the prior art. One could not have been discouraged by a problem if one did not know there was a problem.

Second, as stated above, Applicant's argument rests on the premise that one of skill in the art would have *assumed* 10^4 copies of template to be the minimum amount of template that would allow visualization of the amplified product of that template directly on a gel, because that is the copy number of the β-globin gene amplified by Cheng. However, nowhere is it stated by Cheng that this is the minimum copy number of template that can produce enough amplified product to visualize directly on a gel. Indeed, in the same figure (figure 5), Cheng shows that 10^3 copies of a template (lambda phage) produces enough amplified product to see on a gel. This is 10-fold less than the number of copies of β-globin gene amplified. Thus, according to Applicant's reasoning, one would have expected only to need 1/10 X 22.755 µg = 2.2755 µg of genomic DNA to have an equivalent number of copies of any particular TCR rearrangement.

Applicant would likely argue, based on Dr. Pasqual's experiment in the declaration of 01/11/2011, that this would still not have been expected to be successful since, in that experiment, 2 µg (2000 ng) was shown to inhibit the PCR.

However, the prior art had achieved amplification of long fragments visible on a gel using even fewer copies of template. Stewart et al (Genome Research 5:79-88 (1995)) amplified an 8 kb fragment of HPV16 using only 10 copies, and the product was clearly visible on a gel stained with ethidium bromide (figure 1A, lane 1). Ten copies is 1,000-fold lower than the number of copies of β-globin gene amplified and visualized by Cheng. Thus, according to Applicant's reasoning, one would have expected only to need 1/1,000 X 22.755 µg = 0.022755 µg of genomic DNA (or 22.755 ng) to have an

equivalent number of copies of any particular TCR rearrangement. As shown by Applicant's own experiment (figure 1, declaration filed 01/11/2011), this amount of genomic DNA would not have been expected to significantly impact amplification.

Therefore, as the prior art had already succeeded in amplifying an 8 kb fragment from only 10 copies of template, and had successfully observed the amplification product directly on a gel (nearly 10 years before Applicant's filing date), it is respectfully submitted that one of skill in the art would have had a *reasonable* expectation of success in modifying Pasqual's amplification parameters according to the teachings of the prior art, specifically the parameters discussed in Kolmodin, in order to optimize yield and allow direct visualization of these long amplification products directly on the gel as recited in the claimed methods. Thus, Applicant's arguments are not found persuasive and the rejections are maintained.

In addition, the Examiner would like to revisit the question: what is the relevant difference that allows Applicant's method to produce products directly visible on a gel, whereas the method disclosed in the Pasqual reference does not? The only relevant distinction between the method *as claimed* in claims 23 and 24 is that more than one of the extension steps is carried out for at least 10 minutes, whereas in Pasqual only one, final extension was carried out for at least 10 minutes. If that is the only difference that enables visualization of the products directly on a gel, then the rejection is proper because the prior art suggested longer extension times within the claimed range of "at least 10 minutes". In the declaration provided 04/29/2010, there was a comparison between what was referred to as "Pasqual et al. conditions" and "Instant invention

conditions". However, as discussed previously (Office action of 07/13/2010, page 22-24) it is not clear whether this was an accurate comparison between the claimed method and the method of Pasqual reference (i.e. where the only thing that differed was the use of 10 minute extension steps). There was not sufficient information provided to determine what differed between the two procedures shown in items 9 and 10 of that declaration.

For the reasons discussed above, the rejections are still considered proper and are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Primary Examiner